

### Remarks

Claims 43-78 were pending in the subject application. Applicants have not amended the claims by this Response. Accordingly, claims 43-78 remain before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, and the obviousness-type double patenting rejection.

Claims 43 and 45 are rejected under 35 U.S.C. § 102(b) as anticipated by Ammar *et al.* (1994). The Office Action states that Ammar *et al.* teach the water solubility of carbamazepine in the presence of nicotinamide. Applicants respectfully assert that the Ammar *et al.* reference does not anticipate the claimed invention. Anticipation requires that the reference teach every element of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (1<sup>st</sup> ed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.") Ammar *et al.* do not disclose a co-crystal as required by the claims. A co-crystal is "crystalline material" as defined at page 10 of the specification. One of ordinary skill would recognize that the carbamazepine dissolved in solvent and nicotinamide dissolved in solvent as taught by Ammar *et al.* are not a co-crystal, even if it were assumed for the sake of argument that some interaction might occur between individual dissolved molecules.

Separately, Applicants note that hydrogen bonding is required in the co-crystal (see page 10, line 26, *et seq*) and it is doubtful that the solution disclosed in Ammar *et al.* contains direct or indirect hydrogen bonding between carbamazepine and nicotinamide. Were carbamazepine and nicotinamide to hydrogen bond to one another, each would have fewer hydrogen bond acceptors and/or donors with which to interact with the aqueous solvent and would consequently display to the aqueous solvent a relatively decreased amount of hydrophilic surface area (*i.e.*, hydrogen bond donors and acceptors) and a relatively increased amount of hydrophobic surface area (*i.e.*, aromatic carbon rings). One of skill in the art would recognize that this would tend to decrease solubility in water, as opposed to the increase in solubility that was observed by Ammar *et al.* If a solubility-increasing interaction between carbamazepine and nicotinamide exists, it is more likely that the interaction is between the hydrophobic (non-hydrogen bonding) regions of each. The interaction

would then have the potential to decrease the amount of hydrophobic surface area displayed to the aqueous solvent, and one of ordinary skill would recognize that this might result in increased solubility in water. For each of these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Claims 43, 49, 61 and 67 are rejected under 35 U.S.C. § 103(a) as obvious over de Jong *et al.* (1999). The Office Action indicates that de Jong *et al.* teach lotion formulations comprised of 5-fluorouracil and urea. Applicants respectfully assert that the claimed invention is not obvious over the cited reference. Applicants note that the asserted reference(s), when combined, must teach all elements of the claimed invention. *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2004) (determination of non-obviousness was proper when “no combination of the prior art, even if supported by a motivation to combine, would disclose all the limitations of the claims”). Just as in *CFMT*, Applicants do not believe that all the limitations of the claims are disclosed. De Jong *et al.* do not disclose a co-crystal as required by the claims. A co-crystal is “crystalline material” as defined at page 10 of the specification. In contrast, the lotion formulation of de Jong *et al.* is a solution of propylene glycol and urea in water. (de Jong *et al.*, page 314, first column, second paragraph). One of ordinary skill would recognize that the dissolved 5-fluorouracil and dissolved urea taught by de Jong *et al.* are not a co-crystal. Even if it were assumed for the sake of argument that 5-fluorouracil and urea may hydrogen-bond under some conditions, the ordinarily skilled artisan would recognize that transient hydrogen bonding between isolated dissolved molecules of 5-fluorouracil and urea would not imply the existence of a co-crystal.

Applicants note, too, that obviousness does not exist when the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). In this regard, Applicants assert that de Jong *et al.* teach away from any modification of their own composition that might potentially be encompassed by the claims. As illustrated by the figures at page 316 and the discussion at 317, de Jong *et al.* found that the urea-containing lotion vehicle alone was fully as effective without the added 5-fluorouracil as with it. Indeed, the figures indicate that to the extent there was any difference between vehicle alone and vehicle with 5-fluorouracil, it was vehicle alone that gave the better result. Accordingly, one of ordinary skill would be discouraged from making additional compositions containing both 5-

fluorouracil and urea because the urea-containing preparation was at least as effective without the added 5-fluorouracil and avoided “adverse effects” associated with the “irritating” presence of 5-fluorouracil. (de Jong *et al.* at page 317, last paragraph of the Discussion section). De Jong *et al.* conclude that “the vehicle Belanyx was shown to be preferable over the 1% 5-fluorouracil Belanyx preparation.” For each of the preceding reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 44, 46-48, 50-60, 62-66, and 68-78 are objected to as being dependent on rejected claims. In light of the arguments presented above, Applicants believe that the referenced independent claims are allowable and that the dependent claims are therefore proper. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

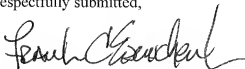
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants’ agreement with or acquiescence in the Examiner’s position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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